**Arnot Ogden Medical Center**

**(In affiliation with the**

**Lake Erie College of Osteopathic Medicine)**

**Research Proposal – A-21-04**

**Sample of a prospective study**

**proposal, including consent form**

**(Edited to serve as an example)**

**Part 1 - Cover Material**

1. Title of project- *A Clinical Evaluation of COVID-19 Vaccine Immunogenicity in Rheumatologic Disease on DMARD Therapy*
2. Names of authors with institutional affiliations.
	1. **PRINCIPAL INVESTIGATOR: 󠄀** James Freeman, MD, Adjunct Clinical Assistant Professor, LECOM, Rheumatologist, Arnot Health [Contact info: James.Freeman@arnothealth.org or 607-737-4100]
	2. **ADDITIONAL INVESTIGATOR(S):** Nedal Darwish, MD PGY-1, Ganesh Arun, DO PGY-1, Manav Bandlamudi, MD PGY-3, Sameer Jhaveri, MS-1 LECOM-Elmira.
	3. Research Coordinator: Uma Yoganathan, MD

CITI training status of all listed investigators is pending.

1. IRB status: will require expedited IRB approval, which is pending.

**Part 2 – Nature of the project**

Research question (s) –

* + - 1. To evaluate the effect of DMARD (methotrexate, adalimumab, etanercept) therapy on the immunogenicity of the COVID-19 vaccine, comparing both monotherapy vs combination therapy in Rheumatoid Arthritis and Psoriatic Arthritis.
1. To evaluate if rheumatologic disease activity alters vaccine immunogenicity.
2. To evaluate if rheumatic disease activity is altered by temporary interruption of therapy at the time of vaccination.

Study design-

1. This will be a prospective observational study of a cohort of patients with a history of rheumatoid arthritis or psoriatic arthritis who are on DMARD therapy.
2. Patients will be evaluated by their rheumatologist, who are members of the research team, to assess disease activity using the RAPID 3 score. They will have one scheduled blood draw, three months after their first vaccination. When possible, blood draws will be scheduled to coincide with patients’ regular routine laboratory monitoring. To be clear, vaccination itself is not the intervention as vaccination is currently recommended by the United States Center for Disease Control and the American College of Rheumatology.
3. Patients will be in groups depending on their current and active DMARD therapy, including monotherapy vs combination therapy.
4. There will be a subset of patients who will have immunosuppressive therapy discontinued for two weeks post-immunizations, and another subset that will continue immunosuppressive therapy continuously throughout immunizations. These patients will be divided into these two groups based upon the preferences of their clinicians. This preference is independent of the study and would have been made regardless. The existence of this study does not affect whether a patient will or will not have a pause in their immunosuppressive therapy. This study is observational. There are currently no guidelines on holding vs continuing immunosuppressive therapy, but literature suggests that there is no increased risk of disease flare with holding medication (7), thus this decision is at the discretion of the treating physician.

1. There will be no additional costs to the patient for the tests being run.
2. The study will use two tests, both of which are drawn at the same time. The first to be analyzed is SARS-COV-2 Antibodies assay (8), which is an assay specifically designed to asses for prior COVID-19 infection. This assay will not detect antibodies induced by SARS-COV-2 vaccines, thus will not be positive post vaccination except if there was a COVID-19 infection. If participant tests positive for previous COVID-19 infection, they will be removed from the study. Next, we will utilize the LabCorp’s Cov2Quant™ IgG assay, “which is available only for use in clinical trials and research, was developed to specifically detect and quantify antibodies to SARS-CoV-2, the virus that causes COVID-19. The level of antibodies is an important indicator of the strength of a person’s immune response, which can help determine the effectiveness of vaccines and therapies. Other COVID-19 antibody tests available in the market are qualitative and detect the presence of antibodies, but do not provide information on the individual’s antibody levels.” (1) We have already been in touch with Labcorp Director of Medical Science, Dr. Jane Yang, and the test is available to this research team.

Inclusion criteria:

1. Male and female patients, aged 18-90 years old, in any distribution
2. Diagnosis of Rheumatoid or Psoriatic arthritis on DMARD therapy
3. Consent and compliance with all aspects of the study protocol, methods, providing data during follow up contact

Exclusion criteria:

1. Male and female patients below age 18, or older than age 90
2. Involvement with any other ongoing studies
3. Pregnancy, which will be self-reported. If a study subject becomes positive, they will be removed from the study.
4. Serologic evidence of prior COVID infection, using the SARS-COV-2 antibodies test obtained during the blood draw, or any other self-reported positive COVID test

Primary outcome measures:

To measure the quantity of IgG antibodies to COVID-19 spike protein produced by the patients based on therapeutic group and disease activity and severity. This will be reported numerically by the Cov2Quant assay. This study aims to help patients and their physicians make informed decisions on the timing of their vaccines in relation to their therapy and the extent of their disease severity. Ideally, our data may be able to contribute to the development of guidelines for the optimal use of the mRNA COVID-19 vaccines in patients with Rheumatoid or Psoriatic arthritis on treatment with the DMARD being studied.

**Part 3 – Literature Background**

Rheumatoid and psoriatic arthritis are the two most common forms of inflammatory arthritis affecting over 2% of the US population (2). Conventional disease modifying agents (cDMARD’s), biologics, and JAK inhibitors are the primary agents used in the treatment of these conditions. Patients with inflammatory arthritis have an increased risk of infections (3), making vaccinations an important part of their management. The effect of the agents used to treat inflammatory arthritis has the potential to blunt the immune response and subsequent efficacy of vaccinations. In fact, methotrexate and rituximab have been shown to blunt the serologic response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis (4). Tofacitinib, a JAK inhibitor, may attenuate the response to pneumococcal vaccine (5). TNF blockers have not been shown to have this effect, but may decrease the response to hepatitis B vaccine (4).

mRNA vaccines are a novel approach to vaccination, and are the only currently available agents for the prevention of COVID-19 viral infection (6). There is little data on the effect of the immune modifying agents used to treat inflammatory arthritis on the immune response to these vaccines. Therefore, guidelines on the need to adjust such therapy at the time of administration of these vaccines are unavailable. Methotrexate, a cDMARD, and etanercept and adalimumab, both TNF inhibitors, are three of the most widely used agents to treat rheumatoid and psoriatic arthritis. We propose to study the seroconversion response to the COIVID-19 mRNA vaccines from Pfizer and Moderna in patients with rheumatoid and psoriatic arthritis on treatment with these agents.

It is suggested a two-week discontinuation period of methotrexate after the administration of the quadrivalent influenza vaccine results in a significantly increased satisfactory immune response compared to continuous therapy, without a significant increase in disease flares. (7) There are no guidelines or studies that exist regarding the continuation or discontinuation of immunosuppression during COVID-19 vaccination.

**Part 4- Risks/Benefits**

1. There is minimal risk involved in the phlebotomy process for obtaining blood samples. All blood draws will be done by laboratory personnel or other individuals duly credentialed and trained in safely obtaining blood specimens.
2. There is also a risk of breaching a patient’s privacy. This will be minimized as described in the section below.

**Part 5 –Privacy Considerations**

1. Data will be recorded in a password protected excel spreadsheet. Patient identification numbers will be used in place of patients’ names to deidentify participant data. Participants will be assigned patient identification numbers (via a random number generator) before the first period of data collection. These identification numbers will be used to label blood specimens to the laboratory, blinding the laboratory to patient group and other information. The researchers will create a participant-identification number key (in a different password protected excel document) to connect participants to their respective pseudonyms. This key will be the only document that contains the real names of the participants—the other spreadsheet will use the participants’ respective pseudonyms.
2. These two password-protected excel spreadsheets will be stored on different flash drives in different locations, to minimize the risk of a data breach. The flash drive with the key (hereafter, Flash Drive 1) will be stored in the locked filing cabinet of the principal investigator’s office. The flash drive with the majority of the data (hereafter Flash Drive 2) will be with another member of the research team. Members of the research team will use their personal computers to access Flash Drive 2 and will remove the flash drive from their computers when they are not accessing the spreadsheet or when they are away from their computers. Members of the research team will not leave the Excel document open and visible if they step away from their computers. Efforts will be made to minimize the number of computers used to access documents and the number of times that the second flash drive (with the majority of the data) is transferred between members of the research team--only members of the research team will have access to these documents and their respective flash drives.
3. The only planned time that members of the research team will need to access Flash Drive 1 will be when they are inputting data from the second period of data collection. Access to the participant-pseudonym key at this stage will be necessary to ensure that the data is connected with the correct participant. Extra precaution will be taken at this stage of data collection—this “pairing” of data to participant will take place in the office of the principal investigator, so that travel with Flash Drive 1 and the time that both flash drives will be together will be minimized. While inputting data from the survey (from the second period of data collection), members of the research team will replace any mention of participants’ names with their respective pseudonyms.

**Part 6 – Additional Forms –** Consent form attached.

**Part 7 – Financial Considerations:**

Labcorp has preliminarily agreed to provide perform and analyze the assay for the research project. LECOM and Arnot GME funds will be applied to for the remaining costs of the project.

**Part 8 – Consent process, if applicable**

Informed consent will be obtained prior to each participant in the study. This will be a self-review prompt that the individual participant will read and either agree or disagree with first/last name and signature prior to proceeding with the study. Dr. Freeman and the IRB board will be available to answer/address any of the participants’ questions/concerns. (Consent form follows below).

**Part 9 – Waiver of informed consent, if applicable – N/A**

**References**

1. October “News and Information on COVID-19.” Labcorp Press Release, 2020, www.labcorp.com/coronavirus-disease-covid-19/news/labcorp-launches-quantitative-antibody-test-assess-effectiveness-covid-19-vaccines-clinical-trials.

2. Merola JF, Espinoza LR, Fleischmann R. Distinguishing rheumatoid arthritis from psoriatic arthritis. RMD Open. 2018;4(2):e000656. Published 2018 Aug 13. doi:10.1136/rmdopen-2018-000656

https://rmdopen.bmj.com/content/rmdopen/4/2/e000656.full.pdf

3. De Camargo MC, Barros BCA, Fulone I, et al. Adverse Events in Patients With Rheumatoid Arthritis and Psoriatic Arthritis Receiving Long-Term Biological Agents in a Real-Life Setting. Front Pharmacol. 2019;10:965. Published 2019 Sep 11. doi:10.3389/fphar.2019.00965

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6749844/

4. Rahier JF, Moutschen M, Van Gompel A, et al. Vaccinations in patients with immune-mediated inflammatory diseases. Rheumatology (Oxford). 2010;49(10):1815-1827. doi:10.1093/rheumatology/keq183

https://pubmed.ncbi.nlm.nih.gov/20591834/

5. Alvin Lee Day, Kevin L. Winthrop, Jeffrey R. Curtis Cleveland Clinic Journal of Medicine Nov 2020, 87 (11) 695-703; DOI: 10.3949/ccjm.87a.20056

https://www.ccjm.org/content/87/11/695

6. Pardi, Norbert et al. “Nucleoside-modified mRNA vaccines induce potent T follicular helper and germinal center B cell responses.” The Journal of experimental medicine vol. 215,6 (2018): 1571-1588. doi:10.1084/jem.20171450

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5987916/>

7. Mehta P, Sanchez E, Moraitis E, et al. Influenza vaccination and interruption of methotrexate in adult patients in the COVID-19 era: an ongoing dilemma. Lancet Rheumatol. 2021;3(1):e9-e10. doi:10.1016/S2665-9913(20)30392-1

**CONSENT FORM:**

**SARS-CoV-2 Antibody Response Post COVID-19-Vaccination in Patients on Immunomodulator Therapy**

**Arnot Ogden Medical Center**

**600 Roe Ave.**

**Elmira, NY 14905**

Consent to Participate in a Research Study

*Concise overview: This is a research study to figure out the effects that certain medications have on how your body responds to the COVID-19 vaccine. If you agree to participate, your blood will be drawn once to have a lab test done on it: three months after your first dose of the COVID-19 vaccine. Participating in this study is of no cost to you. There are no side effects to taking part in this study. Risks of the study are reactions to blood draws, which include bleeding, bruising, skin rash, skin irritation, soreness, or lightheadedness, all of which are extremely rare.*

We are doing a study to see how immunomodulatory medicines (medicines that change how your body fights against infections) affect a person’s response to the COVID-19 vaccine. Our anticipated number of study subjects is 50 persons.

Taking part in this study is completely voluntary and will not cost you anything. The quality of your health care will not be affected by your participation in this study and your doctor will be treating your condition as he or she ordinarily would. Only individuals who have been vaccinated or are to be vaccinated against COVID-19 are being asked to participate in this study. The COVID-19 vaccination itself is not part of the study. Your immunomodulatory medicine (either methotrexate, adalimumab, or etanercept) may or may not be stopped for a brief period following your vaccination; this decision rests with your Rheumatologist and is unrelated to your participation in this study. If you become pregnant during this study, you will be required to report this finding to the study researchers.

We are doing this study to see if being on immunomodulatory medicines affects a person’s antibody (proteins in your blood that help you fight an infection) levels after getting the COVID-19 vaccination. To do this we will do a blood test (SARS-CoV-2 antibodies test) to check your level of antibodies to the COVID-19 virus. If your first SARS-CoV-2 test is positive (which would mean that you had the COVID-19 virus before), we will remove you from the study.

The research study will anonymously use the information from your laboratory values to compare to the laboratory results of other participants and to people who are not taking immunomodulatory medications, who will also be anonymous. Some information may also be taken from your EHR (Electronic Health Records).

The data that will be collected for use in this study include your:

1. Age

2. Sex

3. RAPID3 score (a written score to determine the amount of activity of your rheumatologic disease if you have one, which will be done during a visit with your Rheumatologist)

4. Whether or not you are taking NSAIDs (Nonsteroidal anti-inflammatory drugs)

5. Whether or not you are taking prednisone

6. Whether or not you have Psoriasis

7. Whether or not you had a systemic response to the COVID-19 vaccine (fever, chills, body aches)

8. Whether or not there was any change in your autoimmune disease activity after the COVID-19 vaccine

There are no side effects to taking part in this study. There may be some reactions to blood draws. These include: bleeding, bruising, skin rash, skin irritation, soreness, or lightheadedness, all of which are extremely rare. If, during the course of the study, any significant new findings are discovered by the research team that would influence your decision to continue to participate in the study, these would be relayed to you.

Your participation is completely voluntary. You may withdraw at any time without penalty or changes in your routine treatment. You may be removed from this study by the study researchers if:

1. Your study medication is discontinued by your doctor
2. If you become pregnant during the study
3. If you are infected with COVID-19 during the study (antibody or PCR confirmed)

All information obtained in this study will be kept strictly confidential and anonymous. Data will be recorded in a spreadsheet and the documents will be password protected. Efforts will be made to minimize the number of computers used to access documents. Pseudonyms will be used in place of your name to de-identify your data. Participants will be assigned pseudonyms with a random name generator and the participant-pseudonym key will be saved as a password-protected document on a separate flash drive, to minimize the risk of a data breach. All research results will not include any identifying information. After identifiers are removed from identifiable private information or biospecimens, those information or biospecimens may be retained and then used in future research. Your data and/or biospecimens will not be used for commercial profit. All specimens collected will be maintained for a short period following the study, in case confirmation of results is needed, and then will be destroyed. The results of this study will be communicated to you via phone, email, or through your regular scheduled physician office visit.

If you have any questions about this study, or if you believe that you have suffered a research-related injury, please contact: Nedal Darwish, MD at nedal.darwish@arnothealth.org (607-737-4100); Ganesh Arun, DO at ganesh.arun@arnothealth.org (607-737-4100); or James Freeman, MD at james.freeman@arnothealth.org (607-734-1581). For questions about your rights as a research subject, please contact Irv Freeman, Ph.D., J.D., Chair of the LECOMT Institutional Review Board, at IRBLECOM@lecom.edu or 724-552-2889.

By signing this consent form, you are letting us know that you understand the above information and agree to participate in the study.

**Participant Signature**: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Date**: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_